ORIGINAL ARTICLE

Diagnostic and prognostic impact of copeptin and high-sensitivity cardiac troponin T in patients with pre-existing coronary artery disease and suspected acute myocardial infarction

Mihael Potocki,[1] Tobias Reichlin,[1,2] Simone Thalmann,[1] Christa Zellweger,[1,3] Raphael Twerenbold,[1,3] Miriam Reiter,[1,3] Stephan Steuer,[4] Stefano Bassetti,[5] Beatrice Drexler,[1,3] Claudia Stelzig,[1,3] Michael Freese,[1,3] Katrin Winkler,[6,7] Philip Haaf,[1,3] Cathrin Balmelli,[1,3] Willibald Hochholzer,[3] Stefan Osswald,[1] Christian Mueller[1,3]

► Additional materials are published online only. To view these files please visit the journal online (http://heart.bmj.com/content/98/7.toc).

[1]Department of Cardiology, University Hospital Basel, Basel, Switzerland
[2]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3]Department of Internal Medicine, University Hospital Basel, Basel, Switzerland
[4]Emergency department, Limmattalspital Zürich, Zürich, Switzerland
[5]Department of Internal Medicine, Kantonsspital Olten, Olten, Switzerland
[6]Servicio de Pneumologia, Hospital del Mar - IMIM, UPF, CIBERES, ISC III, Barcelona, Spain
[7]Servicio de Urgencias, Hospital del Mar - IMIM, Barcelona, Spain

Correspondence to
Professor Dr Christian Mueller, Department of Cardiology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland; muellerch@uhbs.ch

Accepted 5 January 2012
Published Online First 15 February 2012

ABSTRACT

Objective The early diagnosis of acute myocardial infarction (AMI) can be particularly challenging in patients with known coronary artery disease (CAD) due to pre-existing ECG changes and chronic increases in cardiac troponin (cTn) levels.

Design Of 1170 consecutive patients presenting with symptoms suggestive of AMI, 433 (37%) with pre-existing CAD were analysed in a prospective multicentre study and the diagnostic and prognostic impact of copeptin in combination with either fourth generation cardiac troponin T (cTnT) or high-sensitivity cTnT (hs-cTnT) was evaluated.

Results AMI was the final diagnosis in 78 patients with pre-existing CAD (18%). Copeptin was significantly higher in patients with AMI than in those without (26 pmol/l (IQR 9—71) vs 7 pmol/l (IQR 4—16), $p<0.001$). The diagnostic accuracy for AMI as quantified by the area under the receiver operating characteristic curve (AUC) was significantly higher for the combination of copeptin and cTnT than for cTnT alone (0.94 vs 0.86, $p<0.001$). The combination of copeptin and hs-cTnT (0.94) was trending to superiority compared with hs-cTnT alone (0.92, $p=0.11$). The combination of copeptin and the cTn assays was able to improve the negative predictive value up to 99.5% to rule out AMI. Copeptin was a strong and independent predictor of 1-year mortality (HR 4.18—4.63). Irrespective of cTn levels, patients with low levels of copeptin had an excellent prognosis compared with patients with raised levels of both copeptin and cTn (360-day mortality 2.8—3.6% vs 23.1—33.8%, $p<0.001$).

Conclusion In patients with pre-existing CAD, copeptin significantly improves the diagnostic accuracy if used in addition to cTnT, but only trended to superiority compared with hs-cTnT alone. Copeptin provides independent prognostic information, largely by overcoming the challenging interpretation of mild increases in hs-cTnT.

Clinical trial registration number ClinicalTrials Gov number NCT00470587.

Coronary artery disease (CAD) is estimated to affect 16.3 million people in the USA; of these, nine million have angina pectoris and nearly eight million have had an acute myocardial infarction (AMI).[1] The rapid and accurate diagnosis of AMI is critical for the initiation of effective evidence-based medical management and treatment,[2 3] but there is still an unmet clinical need. Delayed 'rule in' increases morbidity and mortality, particularly in patients with pre-existing CAD.[4 5] Delayed 'rule out' prolongs the time spent in the emergency department (ED), increasing patients' uncertainty and anxiety and resulting in a significant cost to the healthcare system.[6]

Patients with pre-existing CAD merit particular attention. First, they are at increased risk of AMI as well as anxiety related to non-cardiac causes of chest pain. Second, the impact of myocardial loss is particularly devastating when the myocardium has already had previous assaults, so delayed diagnosis of AMI yields especially severe consequences.[4 5] Third, pre-existing ECG changes are common and render the diagnostic use of the ECG more challenging. Fourth, increased levels of sensitive cardiac troponin (cTn) assays, a new diagnostic option with a lower limit of detection (LoD) below the 99th percentile of a normal reference population and improved precision, have been found in more than 10% of patients with stable CAD.[7–11]

Recently, first pilot studies have investigated the diagnostic and prognostic value of copeptin, the C-terminal part of vasopressin, as a novel sensitive marker of endogenous stress in patients with acute chest pain or established AMI.[12–15] These investigations substantiated the hypothesis that the combination of two different pathophysiological processes quantified by cTn and copeptin might overcome some of the limitations of cTn alone.[12–16] It is not known whether the additional use of copeptin would help to improve the early diagnosis and risk stratification of patients with pre-existing CAD.

METHODS

Study design and population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation Study is an ongoing prospective international multicentre study designed

and coordinated by the University Hospital Basel. From April 2006 to June 2009 a total of 1247 consecutive patients presenting to the ED with acute chest pain with an onset or peak within the last 12 h were recruited. Patients with end stage renal failure were excluded. Pre-existing CAD was defined as a history of previous AMI, previous coronary revascularisation for obstructive CAD or known coronary artery stenosis exceeding 50%. A total of 1170 patients had baseline values of the investigational biomarkers available and were included in the current analysis.

Routine clinical assessment

All patients underwent an initial clinical assessment that included history taking, a physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood tests and chest radiography. Cardiac troponin I (CTnI) or cardiac troponin T (cTnT), creatine kinase-MB (CK-MB) and myoglobin were measured at presentation and 6–9 h after presentation or as long as clinically indicated. The precise timing of clinical post-baseline measurements and the treatment of patients were left to the discretion of the attending physician.

Adjudicated final diagnosis

To determine the final diagnosis for each patient, two independent cardiologists reviewed all available medical records—clinical history, findings on physical examination and results of laboratory tests (including cTn values obtained at the participating hospitals but not those being assessed as part of this study), radiological testing, ECG, echocardiography, cardiac exercise test, coronary angiography—from the time of the patient's arrival in the ED to the end of the 60-day follow-up period. When there was disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

An AMI was defined in accordance with current guidelines.[17] In brief, an AMI was diagnosed when there was evidence of myocardial necrosis in association with clinical signs of myocardial ischaemia. Necrosis was diagnosed by a rising and/or falling pattern of the local cTn level with at least one value above the 99th percentile at a level of imprecision of <10%.[7 18] In the absence of uniformly accepted published guidelines, a significant rise and/or fall was defined as a change of at least 30% in the 99th percentile (or the 10% coefficient of variation (CV) level, respectively) within 6–9 h. The following cTn assays were used for the adjudication of the final diagnosis at the participating hospitals: Axsym cTnI ADV (Abbott, Laboratories, Chicago, Ill., USA), Accu cTnI (Beckman Coulter Inc., Fullerton, CA, USA) and Roche cTnT (Roche, Diagnostics, Mannheim, Germany). All three are well-validated current cTn assays with comparable performance in the diagnosis of AMI (see appendix in online supplement for details on use of local cTn assays for final diagnosis adjudication).[7 18] Unstable angina was diagnosed when a patient had normal cTn levels and typical angina at rest, deterioration of a previously stable angina in cases of positive cardiac exercise testing or cardiac catheterisation showing coronary arteries with stenosis of 70% or more of the vessel diameter or when the diagnosis was uncertain but follow-up information showed that the patient had an AMI or a sudden unexpected cardiac death within 60 days after presentation. Further predefined diagnostic categories included cardiac but not coronary symptoms (eg, perimyocarditis or tachyarrhythmias), non-cardiac causes and symptoms of unknown origin. If AMI was ruled out in the ED but no further diagnostic procedures were performed that were sufficient to establish a conclusive diagnosis, the symptoms were classified as being of unknown origin.

Follow-up and clinical endpoints

After hospital discharge, patients were followed after 3 and 12 months by telephone or in written form. Any clinical (cardiovascular) events since presentation to the ED were collected by establishing contact with the patient and his family physician. Information about death was also obtained from the national registry on mortality.

Outcomes

The primary diagnostic endpoint was the diagnosis of AMI by cTnT, high-sensitivity cTnT (hs-cTnT) and copeptin and their combination. The primary prognostic endpoint was death from all causes. The secondary endpoint was a composite of all-cause death or first AMI in patients with chest pain without AMI as the index event.

Copeptin and cardiac troponin T analysis

Blood samples for determination of copeptin were collected at the time of the patient's presentation to the ED in tubes containing potassium EDTA and in tubes containing serum for assay of fourth generation cTnT (Roche cTnT) and hs-cTnT.[19 20] After centrifugation, samples were frozen at −80°C until they were assayed in a blinded fashion in two batches in a dedicated core laboratory.

Copeptin was measured using a novel commercial sandwich immunoluminometric assay (BRAHMS LUMItest CT-proAVP; BRAHMS AG, Hennigsdorf/Berlin, Germany), as described in detail elsewhere.[21] Since this initial publication, the assay was modified as follows: the capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137–144 (GPAGAL) of proAVP. This modification improved the sensitivity of the assay. The lower detection limit was 0.4 pmol/l and the functional assay sensitivity (<20% interassay CV) was <1 pmol/l. The median copeptin level in 200 healthy persons was 3.7 pmol/l and the 97.5th percentile was 16.4 pmol/l. Based on a reference population of 5000 individuals in the Gutenberg Heart Study, a copeptin level of 9.8 pmol/l corresponds to the 95th percentile and 13 pmol/l to the 97.5th percentile.[14] The selected diagnostic and prognostic cut-off point for copeptin of 9 pmol/l was based on our own previous study results.[13]

All Roche assays were performed with the use of the Elecsys 2010 system (Roche Diagnostics): cTnT with a LoD of 0.01 μg/l, a 99th percentile cut-off point of <0.01 μg/l and a CV of <10% at 0.035 μg/l; hs-cTnT with a limit of blank of 0.003 μg/l, a LoD of 0.005 μg/l, a 99th percentile cut-off point of 0.014 μg/l and a CV of <10% at 0.013 μg/l.[22]

Statistical analysis

Continuous variables are presented as mean±SD or median (IQR) and categorical variables as numbers and percentages. Continuous variables were compared with the use of the Mann–Whitney U test and categorical variables with the use of the Pearson χ^2 test. Receiver operating characteristic (ROC) curves were constructed to assess the sensitivity and specificity of copeptin and cTn measurements obtained at specific times and to compare their ability to diagnose AMI. Logistic regression was used to combine copeptin and cTn levels at presentation. The comparison of areas under the ROC curves (AUC) was performed as recommended by DeLong *et al*[23] The Kaplan–Meier cumulative survival curves in which patients

were divided into groups with biomarker levels below and above predefined cut-off values were constructed and compared by the log-rank test. We used univariate Cox proportional hazard analysis to compute HRs and 95% CI of potential predictors of death. All significant variables were then tested in a multivariable model using the forward stepwise method. All hypothesis testing was two-tailed and p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS Statistics for Windows V.19.0 and MedCalc software V.10.3.0.

RESULTS

Characteristics of patients

Of the 1247 consecutively enrolled patients, measurements of copeptin and the two investigational cTn assays were obtained at presentation from 1170 patients, of whom 433 (37%) had pre-existing CAD. Patients with pre-existing CAD differed in multiple baseline characteristics from those without pre-existing CAD including higher age, higher prevalence of cardiovascular risk factors, impaired renal function, chronic obstructive pulmonary disease, peripheral arterial disease and stroke, lower heart rate and blood pressure, as well as a higher incidence of pre-existing ECG changes including left bundle branch block and T inversion (table 1).

Patients with pre-existing CAD more often had unstable angina (27% vs 6%, p=0.006) but showed no difference in AMI (18% vs 14%, p=0.59) from patients without pre-existing CAD.

Levels of copeptin, cTnT and hs-cTnT at presentation

Median levels of copeptin, cTnT and hs-cTnT were all significantly higher in patients with CAD than in those without pre-existing CAD (table 2).

The levels of copeptin and the cTn assays according to the final diagnosis and the presence of CAD are shown in figure 1.

Use of individual markers in diagnosis

Among patients with CAD with a final diagnosis of AMI, baseline values were raised in 78.2% for cTnT (>0.01 μg/l), in 93.6% for hs-cTnT (>0.014 μg/l) and in 75.6% for copeptin (>9 pmol/l). The corresponding sensitivities, specificities,

Table 1 Baseline characteristics of patients

	All patients n=1170	CAD n=433 (37%)	No CAD n=737 (63%)	p Value
Age (years)				<0.001
Median	64	72	59	
IQR	51–76	59–79	49–72	
Male gender, n (%)	781 (67)	327 (76)	454 (62)	<0.001
Risk factors, n (%)				
Hypertension	744 (64)	360 (83)	384 (52)	<0.001
Hypercholesterolaemia	523 (45)	305 (70)	218 (30)	<0.001
Diabetes	225 (19)	130 (30)	95 (13)	<0.001
Current smoking	281 (24)	82 (19)	199 (27)	0.002
History of smoking	410 (35)	206 (48)	204 (28)	<0.001
History, n (%)				
Chronic obstructive pulmonary disease	121 (10)	71 (16)	50 (7)	<0.001
Renal insufficiency	123 (11)	92 (21)	31 (4)	<0.001
Peripheral artery disease	80 (7)	59 (14)	21 (3)	<0.001
Previous stroke	69 (6)	34 (8)	35 (5)	0.04
Vital status				
Heart rate (bpm)				
Median (IQR)	76 (66–89)	71 (62–82)	78 (68–92)	<0.001
Systolic blood pressure (mm Hg)				
Median (IQR)	142 (127–160)	139 (124–157)	145 (129–161)	<0.001
Diastolic blood pressure (mm Hg)				
Median (IQR)	84 (74–93)	80 (70–89)	86 (77–96)	<0.001
Body mass index				
Median (IQR)	26 (24–30)	27 (24–30)	26 (24–29)	0.08
ECG findings, n (%)				
Left bundle branch block	42 (4)	25 (6)	17 (2)	0.003
ST segment elevation	62 (5)	19 (4)	43 (6)	0.35
ST segment depression	118 (10)	51 (12)	67 (9)	0.16
T wave inversion	89 (8)	46 (11)	43 (6)	0.004
No significant ECG abnormalities	859 (73)	292 (68)	567 (77)	<0.001
Glomerular filtration rate, ml/min/1.73 m^2				
Median (IQR)	89 (71–107)	80 (61–99)	94 (75–109)	<0.001
Adjudicated final diagnosis, n (%)				<0.001
Acute myocardial infarction	184 (16)	78 (18)	106 (14)	0.59
Unstable angina	164 (14)	118 (27)	46 (6)	0.006
Cardiac symptoms from causes other than CAD	154 (13)	42 (10)	112 (15)	0.59
Non-cardiac causes	565 (48)	149 (34)	416 (56)	<0.001
Symptoms of unknown origin	103 (9)	46 (11)	57 (8)	0.85

CAD, coronary artery disease.

Table 2 Copeptin and troponin levels according to pre-existing CAD

	All patients n=1170	CAD n=433 (37%)	No CAD n=737 (63%)	p Value
Copeptin				
Median (IQR), pmol/l	6.8 (3.5–15.6)	8.8 (4.1–23.1)	6.1 (3.2–12.6)	<0.001
Roche troponin T fourth generation (cTnT)				
Median (IQR), μg/l	≤0.01 (≤0.01–≤0.01)	≤0.01 (≤0.01–≤0.01)	≤0.01 (≤0.01–≤0.01)	0.03
Roche high-sensitive troponin T (hs-cTnT)				
Median (IQR), μg/l	0.009 (0.004–0.024)	0.014 (0.008–0.031)	0.007 (0.003–0.018)	<0.001

CAD, coronary artery disease.

negative and positive predictive values are given in table 3. Among patients without a history of CAD, the baseline values were raised in 83.0% for cTnT, 94.3% for hs-cTnT and 67.9% for copeptin (table 3).

Among patients with CAD with final diagnoses other than AMI, baseline values were raised above the decision cut-off point in 9.9% for cTnT, in 39.7% for hs-cTnT and in 43.7% for copeptin, giving specificities of 90.1, 60.3 and 56.3, respectively (table 3). In contrast, among patients without a history of CAD and with final diagnoses other than AMI, the baseline values were raised in 5.4% for cTnT, 18.2% for hs-cTnT (p<0.001 for comparison of hs-cTnT) and 30.6% for copeptin (table 3). Owing to the higher incidence of increased hs-cTnT levels in non-AMI patients, the cut-off for hs-cTnT of >0.014 μg/l showed a lower specificity for AMI in patients with pre-existing CAD (60%) than in those without (82%). To rule out AMI in patients with pre-existing CAD, the negative predictive values are shown in table 3. The diagnostic accuracy as quantified by the AUC to diagnose AMI was 0.86 (95% CI 0.80 to 0.92) for cTnT, 0.92 (95% CI 0.89 to 0.96) for hs-cTnT and 0.76 (95% CI 0.70 to 0.81) for copeptin.

Use of combined markers in diagnosis

Among patients with CAD with a final diagnosis of AMI, baseline values of either copeptin or cTnT singly or the two combined were raised in 98.7% of patients. The same proportion had raised values when copeptin was combined with hs-cTnT (table 3). Among patients without a history of CAD, the baseline values were raised in 98.1% for copeptin with cTnT and in 99.1% for copeptin with hs-cTnT.

Among patients with CAD with final diagnoses other than AMI, baseline values of either copeptin or cTnT or a combination of the two were raised in 46.5% of patients for copeptin and in 59.6% for hs-cTnT, giving specificities of 53.5 and 41.4, respectively (table 3). In contrast, among patients without a history of CAD and with a final diagnosis other than AMI, the percentage was 33.1% for copeptin with cTnT and 39.9% for copeptin with hs-cTnT (table 3). All negative predictive values are also shown in table 3, with the highest negative predictive value of 99.5 for the combination of copeptin with cTnT.

The combination of copeptin and cTnT significantly increased the diagnostic accuracy provided by cTnT alone to 0.94 (95% CI 0.91 to 0.97, p<0.001; figure 2). The combination of copeptin and the hs-cTnT assay trended to superiority with an AUC of 0.94 (95% CI 0.91 to 0.97) compared with hs-cTnT alone (p=0.11). The diagnostic performance of copeptin and its combination with cTnT and hs-cTnT was similar in patients with and without pre-existing CAD (p=NS for all comparisons; figure 2).

Figure 3 shows the different AUCs among patients with pre-existing CAD who presented at different time points since the onset of chest pain. The difference in AUCs for the different markers was most pronounced in patients who presented within 3 h after onset of chest pain. The AUC of hs-cTnT and the combination of copeptin with either cTnT or hs-cTnT steadily increased with time from onset of chest pain.

Effect of copeptin on prognosis in patients with pre-existing CAD

During a median follow-up time of 497 days (range 376–791), 41 patients died (10%). Baseline copeptin levels were higher

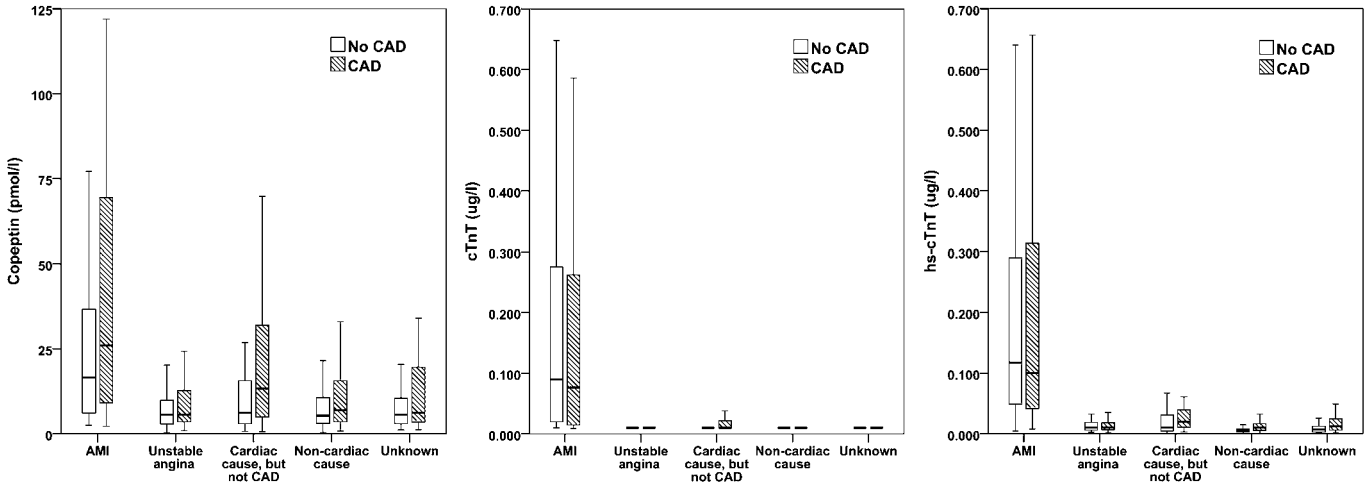

Figure 1 Copeptin and cardiac troponin levels according to the final diagnosis. CAD, coronary artery disease; cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T.

Table 3 Diagnostic performance of copeptin and different troponin assays and their combination at presentation in patients with and without pre-existing coronary artery disease (CAD)

	Sensitivity (95% CI)	Specificity (95% CI)	Negative predictive value (95% CI)	Positive predictive value (95% CI)
Patients with pre-existing CAD				
Copeptin 9 pmol/l (cut-off)	75.6 (64.6 to 84.7)	56.3 (51.0 to 61.6)	91.3 (86.8 to 94.7)	27.6 (21.7 to 34.1)
Roche troponin T fourth generation (cTnT)				
cTnT 0.01 μg/l (cut-off)	78.2 (67.4 to 86.8)	90.1 (86.6 to 93.0)	95.0 (92.1 to 97.0)	63.5 (53.1 to 73.1)
+ Copeptin 9 pmol/l (cut-off)	98.7 (93.0 to 99.8)	53.5 (48.2 to 58.8)	99.5 (97.1 to 99.9)	31.8 (26.0 to 38.1)
Roche high-sensitive troponin T (hs-cTnT)				
hs-cTnT 0.014 μg/l (cut-off)	93.6 (85.7 to 97.9)	60.2 (55.0 to 65.4)	97.7 (94.8 to 99.3)	34.1 (27.8 to 40.9)
+ Copeptin 9 pmol/l (cut-off)	98.7 (93.0 to 99.8)	41.4 (36.2 to 46.7)	99.3 (96.3 to 99.9)	27.0 (22.0 to 32.6)
Patients without pre-existing CAD				
Copeptin 9 pmol/l (cut-off)	67.9 (58.2 to 76.7)	69.4 (65.7 to 73.0)	92.8 (90.1 to 95.0)	27.2 (21.9 to 33.0)
Roche troponin T fourth generation (cTnT)				
cTnT 0.01 μg/l (cut-off)	83.0 (74.5 to 89.6)	94.6 (92.6 to 96.2)	97.1 (95.4 to 98.3)	72.1 (63.3 to 79.9)
+ Copeptin 9 pmol/l (cut-off)	98.1 (93.3 to 99.7)	66.9 (63.1 to 70.5)	99.5 (98.3 to 99.9)	33.2 (28.0 to 38.8)
Roche high-sensitive troponin T (hs-cTnT)				
hs-cTnT 0.014 μg/l (cut-off)	94.3 (88.1 to 97.9)	81.8 (78.5 to 84.7)	98.9 (97.5 to 99.6)	46.5 (39.7 to 52.4)
+ Copeptin 9 pmol/l (cut-off)	99.1 (94.8 to 99.8)	60.1 (56.1 to 63.9)	99.7 (98.5 to 100.0)	29.4 (24.7 to 34.4)

among patients who died in the 360-day period after presentation than in survivors (60 pmol/l (range 14–103) vs 8 pmol/l (range 4–21); p<0.001 for 30-day mortality and 41 pmol/l (range 18–93) vs 8 pmol/l (range 4–18); p<0.001 for 360-day mortality). Kaplan–Meier analysis demonstrated a low 360-day mortality rate of 3.2% in patients with copeptin levels ≤9 pmol/l compared with a mortality rate of 26% in patients with copeptin levels above the cut-off (p<0.001). Kaplan–Meier analyses using strata defined by the cut-off point of cTnT (0.01 μg/l) and the 99th percentile of hs-cTnT (0.014 μg/l) showed that copeptin with a cut-off point of 9 pmol/l clearly separated low- and high-risk patients (figure 4). Irrespective of raised troponin levels, patients with low copeptin levels had an excellent prognosis with a 360-day mortality rate of 2.8% (hs-cTnT >0.014 μg/l) and 3.6% (cTnT >0.01 μg/l), respectively. In contrast, patients with both raised copeptin and troponin levels had a mortality rate of 23.1% (hs-cTnT >0.014 μg/l) and 33.8% (cTnT >0.01 μg/l), respectively (p<0.001 for difference).

Univariable Cox regression analysis confirmed a copeptin level of >9 pmol/l as a strong predictor of mortality (HR 5.4, 95% CI 2.4 to 12.2; p<0.001). In multivariable analysis, together with all significant baseline variables including either cTnT or hs-cTnT, copeptin was the strongest independent predictor. Of note, in the model with hs-cTnT, raised hs-cTnT levels were no longer a predictor of mortality (table 4). Similar findings were obtained in the Cox regression analyses assessing the combined endpoint of death and non-fatal AMI in patients with index diagnoses other than AMI (data not shown).

DISCUSSION

This prospective multicentre study in unselected patients presenting to the ED with acute chest pain examined the value of a dual marker strategy using cTn, a marker of cardiac necrosis, and copeptin, a marker of endogenous stress, for diagnostic and prognostic purposes with a special focus on the important subgroup of patients with pre-existing CAD. We report four major findings: (1) the specificity for the diagnosis of AMI of a raised hs-cTnT level was significantly lower in patients with CAD than in those without CAD (60% vs 82%) because a significant proportion of non-AMI patients had raised hs-cTnT levels (40%); (2) as a stand-alone test, copeptin is inferior to cTnT and hs-cTnT in the diagnosis of AMI but, in combination with copeptin, the diagnostic accuracy significantly increased in

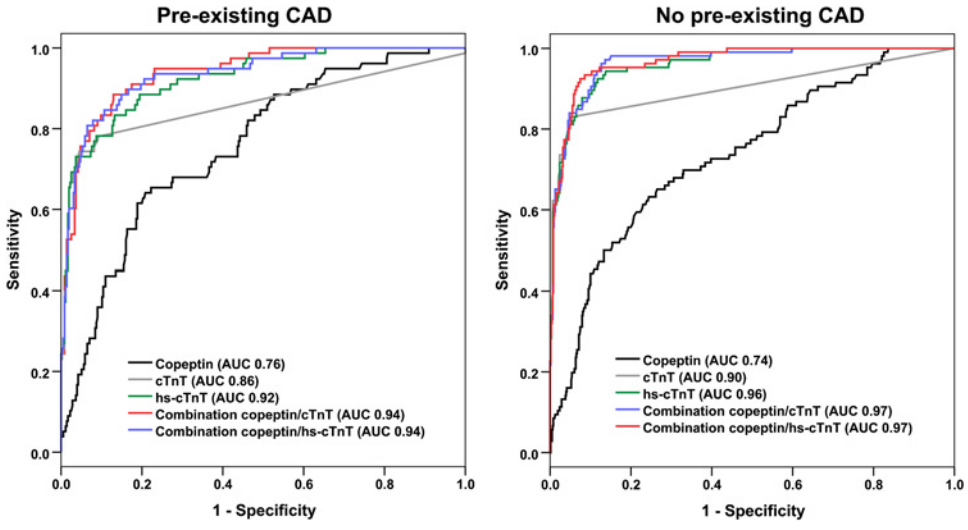

Figure 2 Receiver operating characteristic curves at presentation for the diagnosis of acute myocardial infarction. AUC, area under the curve; CAD, coronary artery disease; cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T.

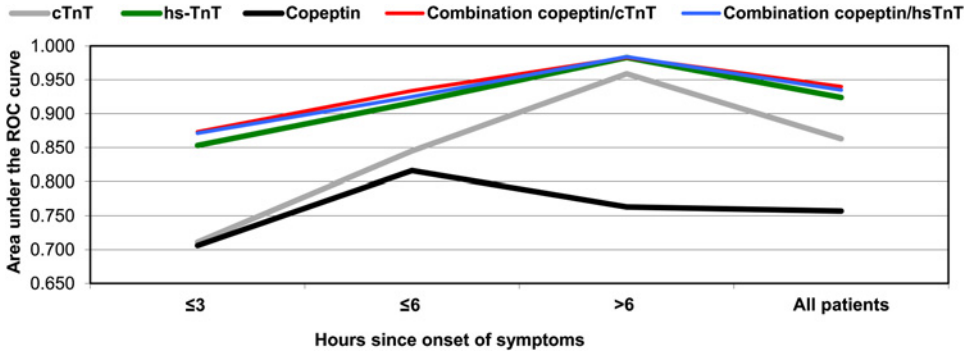

Figure 3 Diagnostic accuracy of copeptin and troponin assays and their combination at presentation according to time since onset of chest pain in patients with pre-existing coronary artery disease (CAD). cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T.

patients with pre-existing CAD; (3) the negative predictive value to rule out AMI at ED presentation improved to 99.5% with cTnT and 99.3% with hs-cTnT in combination with copeptin; (4) copeptin was a powerful independent predictor of mortality. Patients with low copeptin values had an excellent prognosis even with raised levels of cTnT or hs-cTnT, while patients with increased levels of both copeptin and cTn comprised a high-risk population with impaired prognosis.

Our findings extend and corroborate previous studies describing the potential use of copeptin to rule out AMI in patients with acute chest pain and have the potential to improve the diagnosis of AMI and triage of patients with pre-existing CAD at the time of presentation to the ED.[13 24 25] Copeptin, the C-terminal part of vasopressin, is secreted stoichiometrically with arginine vasopressin from the neurohypophysis and plays a crucial role in the regulation of the individual endogenous stress response. Routine measurement of arginine vasopressin in clinical practice has so far been limited because of instability (half-life 5–15 min) and substantial attachment to platelets.[26 27] Copeptin is much more stable, overcoming the limitations and difficulties of assessing the arginine vasopressin system.[21] Our findings show that the benefits of a combination of copeptin with the standard cTnT assay can be extended to the high-risk group of patients with pre-existing CAD. The diagnostic gain when added to hs-cTnT was smaller, which was expected because of the substantially higher diagnostic accuracy of hs-cTnT. With regard to ruling out AMI, the combination of copeptin with hs-cTnT increased the sensitivity from 93.6% to 98.7%, providing an excellent negative predictive value of 99.3%. In contrast, with regard to ruling in AMI, the combination of a positive hs-cTnT and a positive copeptin provided a positive predictive value of only 38% with a specificity of 75%, limiting its value for this purpose. The guidelines for the management of acute coronary syndromes in patients presenting without persistent ST segment elevation recommend serial troponin measurements at presentation and after 3 h.[28] Our results suggest that measuring troponin and copeptin together at presentation might obviate a prolonged stay in the ED. To our knowledge, only one small study has been performed which found that copeptin does not add diagnostic information to patients with acute chest pain.[25] However, a major limitation of the study is the very small number of patients with acute coronary syndrome. Of 366 patients enrolled, only 35 patients had an acute coronary syndrome, of whom 27 were classified as having unstable angina and eight had AMI. Furthermore, blood samples were drawn after a median of 4.5 h, which is too late for patients with chest pain because the ability to rule out myocardial infarction at admission is what clinically matters.

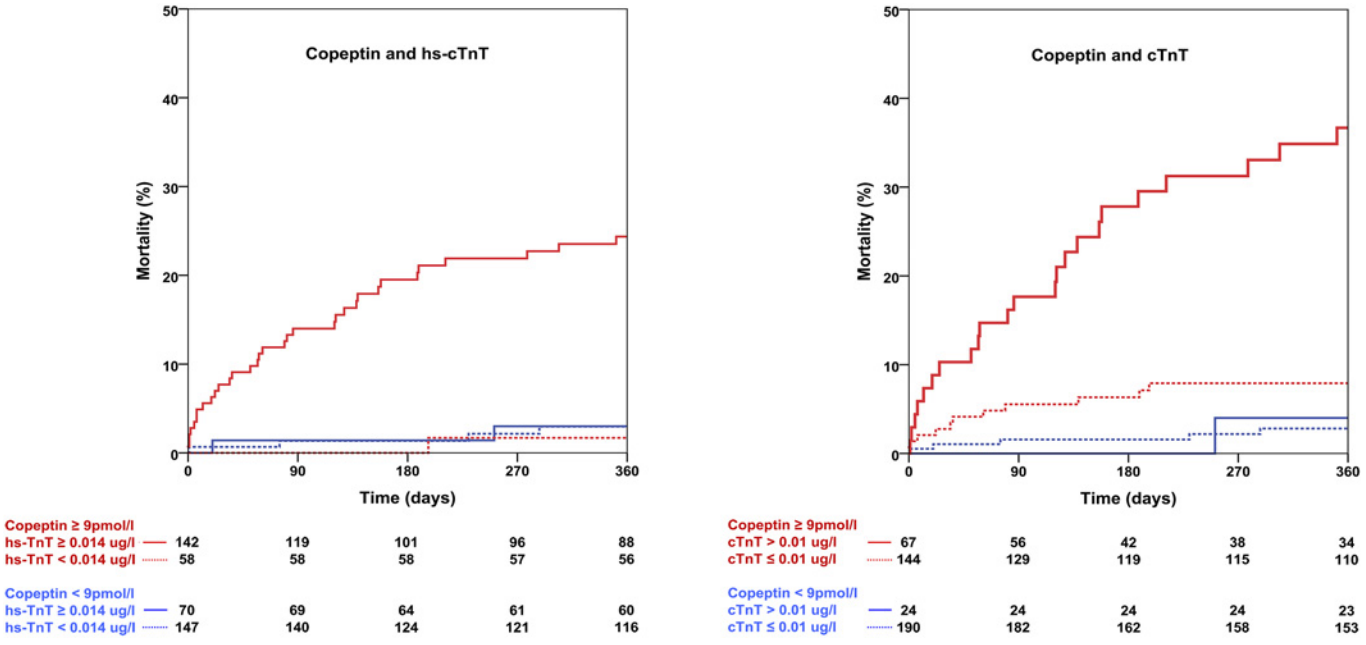

Figure 4 Mortality within 360 days according to copeptin and cardiac troponin cut-off levels. cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T.

Table 4 Multivariate Cox regression analysis for mortality during follow-up

	Univariate		Multivariate			
			Model with hs-cTnT		Model with cTnT	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (years)	1.09 (1.06 to 1.13)	<0.001	1.08 (1.04 to 1.12)	<0.001	1.06 (1.03 to 1.10)	0.001
Gender	1.02 (0.50 to 2.07)	0.97				
Diabetes mellitus	1.72 (0.92 to 3.20)	0.09				
Previous stroke	3.63 (1.73 to 7.60)	0.001				
Heart rate	1.03 (1.02 to 1.04)	0.001	1.03 (1.02 to 1.04)	<0.001	1.02 (1.01 to 1.04)	0.001
Systolic blood pressure	0.98 (0.96 to 0.99)	<0.001				
Diastolic blood pressure	0.95 (0.93 to 0.97)	<0.001	0.95 (0.93 to 0.97)	<0.001	0.95 (0.93 to 0.97)	<0.001
Body mass index	0.90 (0.83 to 0.98)	0.02				
Glomerular filtration rate	0.98 (0.97 to 0.99)	0.001	1.02 (1.00 to 1.03)	0.05	1.02 (1.00 to 1.03)	0.03
hs-cTnT >0.014 μg/l	6.33 (2.66 to 15.04)	<0.001				
cTnT >0.01 μg/l	5.45 (2.93 to 10.15)	<0.001			2.40 (1.15 to 4.99)	0.02
Copeptin >14 pmol/l	5.42 (2.40 to 12.22)	<0.001	4.63 (1.83 to 11.71)	0.001	4.18 (1.64 to 10.61)	0.003

cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T.

In our study, copeptin was a strong and independent prognostic marker in patients with pre-existing CAD. Copeptin levels measured at presentation provided powerful information for the risk of death during the subsequent 12 months. Only patients characterised by both raised copeptin and cTn levels were at markedly increased risk, whereas patients with raised hs-cTnT levels and normal copeptin levels had a similar prognosis to those with normal hs-cTnT levels. This point merits special attention. The clinical use of highly-sensitive cTn assays leads to a marked increase in patients with increased cTn in settings other than AMI.[10 11 29] This has caused some confusion among clinicians and makes the interpretation of raised troponin values more challenging.[30–32] Having a second marker that identifies patients with a good prognosis despite a raised highly-sensitive cTn level is therefore of great clinical value. Copeptin might help emergency physicians to tailor treatment in view of the RR and allocate resources accordingly. Tailored treatment in high-risk patients may include consultation of specialists, early invasive strategy or admission to the intensive care unit. Whether this risk stratification-guided strategy might affect outcome needs to be evaluated prospectively.

Our findings corroborate and extend previous studies investigating the prognostic role of copeptin in different various settings such as AMI, unstable angina and heart failure.[12 15 33–35] Khan *et al* showed that copeptin levels were raised in nearly all patients after AMI and that copeptin levels were closely associated with the risk of death.[12] Interestingly, an animal study documented the release of vasopressin from cardiomyocytes, indicating a vasopressin system in rat hearts.[36] This experiment showed that vasopressin is synthesised and released on stimulation with cardiac pressure overload or stimulation with nitric oxide, resulting in systemic effects such as osmoregulation, regulation of cardiac function, perfusion and cardiac neurohormone secretion. These findings could explain the higher copeptin concentrations in patients with pre-existing CAD even in the absence of AMI because of increased nitric oxide synthesis.[37]

The following limitations of the current study merit consideration. First, we evaluated two cTn assays with widely different sensitivity to examine the added value of copeptin at both ends of the sensitivity spectrum of cTn assays. Whether these findings can be generalised to other cTn assays requires validation in future studies. Second, in this ongoing prospective study, the subgroup analysis of patients with pre-existing CAD was not predefined at the time of the initial protocol written in 2005. It was added while we were still blind to the results in 2009 with regard to previous investigations, challenging the diagnostic accuracy of sensitive cTn assays in patients with pre-existing CAD.[29 38] Third, this observational study cannot quantify exactly the clinical benefit associated with the combination of copeptin and the cTn. Intervention studies are required to obtain this important information.

In conclusion, in patients with pre-existing CAD, the additional use of copeptin seems to be an attractive option to overcome at least some of the limitations of the cTn assay used. When copeptin is used in combination with cTnT, it significantly improved diagnostic and prognostic accuracy, largely by overcoming the sensitivity deficit. The additional use of copeptin results in a very high negative predictive value and seems to allow the rapid rule-out of AMI at presentation. When copeptin was used in combination with hs-cTnT it significantly increased prognostic accuracy, largely by overcoming the challenging interpretation of mild increases in hs-cTnT that are common in patients with chronic cardiac disorders.

Acknowledgements We thank the patients who participated in the study, the staff of the emergency department, the laboratory technicians (particularly Kirsten Hochholzer, Esther Garrido, Irina Klimmeck, Melanie Wieland and Fausta Chiaverio) and Drs C Schindler and K Denhaerynck for expert statistical advice.

Funding This work was supported by research grants from the Swiss National Science Foundation (PP00B-102853), the Swiss Heart Foundation, the University Basel, Abbott, Roche, Nanosphere, Siemens and the Department of Internal Medicine, University Hospital Basel.

Competing interests CM has received speaker honoraria from Abbott, ALERE, BRAHMS, Roche and Siemens. MP has received speaker honoraria from Abbott, BRAHMS and Roche. RT has received speaker honoraria from BRAHMS. The assays were donated by the manufacturers who had no role in the design of the study, analysis of the data, preparation of the manuscript or the decision to submit for publication.

Patient consent Written informed consent approved by the local ethics committees was obtained from all patients.

Ethics approval The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

Contributors MP, TR: analysis and interpretation of data, drafting the article, final approval of the version to be published. ST, CZ, RT, MR, SS, SB, BD, CS, MF, KW, PH, CB, SO: analysis and interpretation of data, revising article critically for important intellectual content, final approval of the version to be published. WH: conception and design, analysis and interpretation of data, final approval of the version to be published. CM: conception and design, analysis and interpretation of data, drafting the article, final approval of the version to be published.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Roger VL,** Go AS, Lloyd-Jones DM, *et al*; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation* 2011;**123**:e18—209.
2. **Anderson JL,** Adams CD, Antman EM, *et al*. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *Circulation* 2007;**116**:e148—304.
3. **Bassand JP,** Hamm CW, Ardissino D, *et al*; Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1598—660.
4. **Antman EM,** Cohen M, Bernink PJ, *et al*. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;**284**:835—42.
5. **Morrow DA,** Antman EM, Charlesworth A, *et al*. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;**102**:2031—7.
6. **Tiemann O.** Variations in hospitalisation costs for acute myocardial infarction - a comparison across Europe. *Health Econ* 2008;**17**(1 Suppl):S33—45.
7. **Apple FS,** Jesse RL, Newby LK, *et al*; National Academy of Clinical Biochemistry; IFCC Committee for Standardization of Markers of Cardiac Damage. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biochemical markers of acute coronary syndromes. *Circulation* 2007;**115**:e352—5.
8. **Apple FS,** Smith SW, Pearce LA, *et al*. Use of the Centaur TnI-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. *Clin Chem* 2008;**54**:723—8.
9. **Melanson SE,** Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. *Am J Clin Pathol* 2007;**128**:282—6.
10. **Keller T,** Zeller T, Peetz D, *et al*. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;**361**:868—77.
11. **Reichlin T,** Hochholzer W, Bassetti S, *et al*. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;**361**:858—67.
12. **Khan SQ,** Dhillon OS, O'Brien RJ, *et al*. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. *Circulation* 2007;**115**:2103—10.
13. **Reichlin T,** Hochholzer W, Stelzig C, *et al*. Incremental value of copeptin for rapid rule out of acute myocardial infarction. *J Am Coll Cardiol* 2009;**54**:60—8.
14. **Keller T,** Tzikas S, Zeller T, *et al*. Copeptin improves early diagnosis of acute myocardial infarction. *J Am Coll Cardiol* 2010;**55**:2096—106.
15. **Narayan H,** Dhillon OS, Quinn PA, *et al*. C-terminal provasopressin (copeptin) as a prognostic marker after acute non-ST elevation myocardial infarction: Leicester Acute Myocardial Infarction Peptide II (LAMP II) study. *Clin Sci (Lond)* 2011;**121**:79—89.
16. **Meune C,** Drexler B, Haaf P, *et al*. The GRACE score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and B-type natriuretic peptide. *Heart* 2011;**97**:1479—83.
17. **Thygesen K,** Alpert JS, White HD, *et al*. Universal definition of myocardial infarction. *Circulation* 2007;**116**:2634—53.
18. **Apple FS,** Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. *Am Heart J* 2002;**144**:981—6.
19. **McCann CJ,** Glover BM, Menown IB, *et al*. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. *Eur Heart J* 2008;**29**:2843—50.
20. **Mingels A,** Jacobs L, Michielsen E, *et al*. Reference population and marathon runner sera assessed by Highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. *Clin Chem* 2009;**55**:101—8.
21. **Morgenthaler NG,** Struck J, Alonso C, *et al*. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem* 2006;**52**:112—19.
22. **Giannitsis E,** Kurz K, Hallermayer K, *et al*. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem* 2010;**56**:254—61.
23. **DeLong ER,** DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;**44**:837—45.
24. **Giannitsis E,** Kehayova T, Vafaie M, *et al*. Combined testing of high-sensitivity troponin T and copeptin on presentation at prespecified cutoffs improves rapid rule-out of non-ST-segment elevation myocardial infarction. *Clin Chem* 2011;**57**:1452—5.
25. **Karakas M,** Januzzi JL Jr, Meyer J, *et al*. Copeptin does not add diagnostic information to high-sensitivity troponin T in low- to Intermediate-risk patients with acute chest pain: results from the rule out myocardial infarction by computed tomography (ROMICAT) study. *Clin Chem* 2011;**57**:1137—45.
26. **Preibisz JJ,** Sealey JE, Laragh JH, *et al*. Plasma and platelet vasopressin in essential hypertension and congestive heart failure. *Hypertension* 1983;**5**:I129—38.
27. **Robertson GL,** Mahr EA, Athar S, *et al*. Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. *J Clin Invest* 1973;**52**:2340—52.
28. **Hamm CW,** Bassand JP, Agewall S, *et al*. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2999—3054.
29. **Omland T,** de Lemos JA, Sabatine MS, *et al*; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 2009;**361**:2538—47.
30. **Lippi G,** Montagnana M, Guidi GC. The clinical dilemma of positive results of high-sensitive troponin assays. *Am J Cardiol* 2009;**103**:1332.
31. **Twerenbold R,** Reichlin T, Reiter M, *et al*. High-sensitive cardiac troponin: friend or foe? *Swiss Med Wkly* 2011;**141**:w13202.
32. **Jaffe AS.** The 10 commandments of troponin, with special reference to high sensitivity assays. *Heart* 2011;**97**:940—6.
33. **Potocki M,** Breidthardt T, Mueller A, *et al*. Copeptin and risk stratification in patients with acute dyspnea. *Crit Care* 2010;**14**:R213.
34. **Staub D,** Morgenthaler NG, Buser C, *et al*. Use of copeptin in the detection of myocardial ischemia. *Clin Chim Acta* 2009;**399**:69—73.
35. **Voors AA,** von Haehling S, Anker SD, *et al*. C-terminal provasopressin (copeptin) is a strong prognostic marker in patients with heart failure after an acute myocardial infarction: results from the OPTIMAAL study. *Eur Heart J* 2009;**30**:1187—94.
36. **Hupf H,** Grimm D, Riegger GA, *et al*. Evidence for a vasopressin system in the rat heart. *Circ Res* 1999;**84**:365—70.
37. **Yoon Y,** Song J, Hong SH, *et al*. Plasma nitric oxide concentrations and nitric oxide synthase gene polymorphisms in coronary artery disease. *Clin Chem* 2000;**46**:1626—30.
38. **Eggers KM,** Lind L, Venge P, *et al*. Will the universal definition of myocardial infarction criteria result in an overdiagnosis of myocardial infarction? *Am J Cardiol* 2009;**103**:588—91.